Relation of Body Fat Distribution to Reproductive Factors in Pre- and Postmenopausal Women

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Abstract

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The cross-sectional relations of several reproductive characteristics with self-reported waist-to-hip circumference ratio were evaluated in 44,487 pre- and postmenopausal women 40 to 65 years of age who were free of cancer, cardiovascular disease, and diabetes. All results were adjusted for age, body mass index, cigarette smoking, physical activity, and alcohol intake. Current use of postmenopausal hormones was associated with a significantly lower waist-to-hip ratio than either past or never use independent of type of menopause (0.778 versus 0.784, p=0.0001 and 0.787, p=0.0001, respectively), although associations with type (unopposed estrogens versus combined estrogen and progesterone) and duration of hormone therapy were not noted. Waist-to-hip ratio did not differ between pre- and postmenopausal women, but demonstrated weak positive associations with age at menarche, parity, and age at first birth, and a weak inverse association with past duration of breast-feeding. These data confirm relations of several reproductive factors and use of hormone replacement therapy with body fat distribution. Epidemiologic studies relating body fat distribution to disease outcomes in women should consider these factors as potential confounders.

Key words: waist-to-hip ratio, fat distribution, reproductive factors, exogenous hormones

Introduction

The importance of the relation of body fat distribution to several diseases and conditions is now widely accepted. Body fat distribution, independent of overall adiposity, is an important risk factor for diabetes (11,18) and cardiovascular disease (16,19) in both men and women. In addition, a recent study among postmenopausal women found a monotonic increase in risk of total mortality associated with increasing central adiposity (7). Fewer studies have assessed factors which may influence the distribution of body fat. This information would be useful for identifying potential confounders of the relation of body fat distribution to disease and, perhaps more importantly, in providing ways to modify fat distribution and thus lower disease risk.

A role for sex hormones in determining the location of fat deposition is strongly suggested by the observation that women tend to accumulate fat in the femoral-gluteal area and men in the abdomen. While data on female sex hormones and fat distribution are generally lacking, studies that have directly assessed level of androgenicity show a positive association with central fat distribution independent of overall adiposity in pre- and postmenopausal women (28,29,10). In contrast, androgenic activity appears inversely predictive of central adiposity in men (24,14).

Processes regulating fat accumulation, such as lipoprotein lipase (LPL) and lipolytic activity, also differ by anatomic region among men and pre- and postmenopausal women. In premenopausal women, basal lipolysis is similar in femoral and abdominal adipocytes but noradrenaline-stimulated lipolysis is significantly greater in the abdominal region (21). Conversely, LPL

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activity is greater in femoral adipocytes, a difference that becomes more pronounced during early pregnancy (21,23). With menopause, the difference in LPL activity between anatomical regions seems to dissipate, (23,20), as does lipolytic responsiveness of abdominal adipocytes (23). Men may have even lower LPL activity in femoral adipocytes than postmenopausal women (23). Taken together, these observations suggest that female sex hormones may influence distribution of body fat in part by enhancing accumulation of fat in the femoral-gluteal area through increased LPL activity, and concomitantly inhibiting accumulation of fat in the abdominal region through increased catecholamine-stimulated lipolysis.

We hypothesized that central adiposity as measured by waist-to-hip ratio would be greater in postmenopausal women compared to premenopausal women, and lower in postmenopausal women using hormone replacement therapy compared to never users. Detailed data on these and additional reproductive factors were available from the Nurses' Health Study (NHS), a large cohort of middle-aged women living in the United States.

Methods

Study Population

The Nurses' Health Study (NHS), established in 1976, consists of 121,700 female, registered nurses who were 30 to 55 years of age at entry. The cohort is 98% Caucasian. Participants completed a baseline questionnaire which provided information on age, height, weight, and reproductive and lifestyle variables. Subsequent questionnaires were completed every two years allowing participants to update their information. Eighty-four percent of the original cohort responded to the follow-up questionnaire in 1986.

A total of 52,029 women reported both a waist and hip circumference on the 1986 NHS questionnaire (53,174 reported a measurement of waist circumference and 52,873 reported a hip circumference). We excluded 91 women from the analysis who reported implausible values for waist or hip circumference. For the present investigation the sample included 44,487 women who were free of angina, cancer, and diabetes, and who had not experienced a myocardial infarction or stroke prior to 1986. Women were excluded on the basis of disease to prevent bias resulting from their proclivity to change behaviors that might be related to body fat distribution. The sample sizes for individual analyses vary slightly due to restriction and missing values.

Anthropometric Measures

Participants were asked to measure and report their waist circumference (at the umbilicus) and hip circumference (at the largest circumference) to the nearest quarter of an inch on the 1986 NHS questionnaire in addition to providing current weight in pounds. Height was reported on the initial (1976) questionnaire in inches and converted to meters. The validity of the self-reported measures was assessed in a subsample of the cohort (25). Self-reported measurements were highly correlated with standardized measurements taken by technicians (r=0.89 for waist, r=0.84 for hip, and r=0.70 for waist-to-hip ratio). Technician-measured weight was also highly correlated with self-reported weight (r=0.97). Waist-to-hip ratio (WHR) was formed by dividing waist circumference by hip circumference. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Menopause and Postmenopausal Hormone Use

Information on menopausal status, and type and duration of hormone replacement therapy (HRT) was requested on each NHS questionnaire since 1976. Characteristics of menopause from 1986 were used for the present analyses. Menopause was defined by the nurse's response to the question, "Have your menstrual periods ceased permanently?" Subsequent questions inquired whether menopause was natural or surgical (with number of ovaries removed), and age at menopause. Women reporting surgical menopause without removal of both ovaries were classified according to their age and smoking status: Nonsmokers were considered premenopausal if they were 48 years of age or younger, and postmenopausal if they were 56 years of age or older. The cutoffs were two years earlier for current smokers (33). Subjects were categorized as perimenopausal if they fell between the cutoffs and were excluded from the menopause analyses (n=2,836). Self-reported menopausal status was highly reproducible in a subsample of the population (5). Age at menopause reported on the 1978 and 1980 questionnaires agreed to within one year for 95% of the 2,315 women reporting incident surgical menopause, and for 82% of the 31,000 women who had experienced natural menopause prior to 1976. Among a random sample of 200 women reporting surgical menopause between 1982 and 1984 there was complete agreement between self-report and medical record for details of hysterectomy and extent of ovarian surgery for all but two women.

Other Reproductive Variables

History of breast-feeding (in total months) was ascertained in 1986. Parity was updated every 2 years until 1984, and age at menarche and age at first birth were obtained from the 1976 questionnaire and updated. Infertility (in 1980) was defined as a positive response to the question, "Have you ever tried to become pregnant for more than two years without success?" A second question allowed us to determine if the cause of infertility was associated with the nurse. Only these cases of infertility were used in the infertility analyses.

Covariates

Cigarette smoking was categorized by present status (never/former/current with six levels of cigarettes smoked per day). A validated (8) semiquantitative food frequency questionnaire administered in 1986 provided information on alcohol intake using separate questions on individual alcoholic beverages (white and red wine, liquor and beer). Alcohol intake was categorized into five groups: nondrinkers, and four groups representing quartiles of the distribution for nurses with nonzero values for alcohol intake. A validated (34) measure of physical activity in metabolic equivalent unit hours per week, available from the 1986 NHS questionnaire, was categorized into quintiles.

Statistical Analysis

Non-parametric Spearman correlations were calculated between the anthropometric variables and continuous variables for age and several of the reproductive factors. Analysis of covariance was used to determine the independent relations of each of the anthropometric measures to the reproductive characteristics. BMI was adjusted for age and WHR, WHR was adjusted for age and BMI, and waist circumference was adjusted for age, BMI and height as a measure of body size. Further analyses were adjusted for cigarette smoking, alcohol intake, and physical activity. Multiple linear regression analysis was used to test for trend and to evaluate interactions.

The natural logarithms of BMI, WHR, and waist circumference were used to improve normality. The exponents of the least-square means for the logarithm-transformed variables were tabulated to facilitate interpretation of the comparisons. The standard errors presented in the tables correspond to the logarithm-transformed variables. Two-sided p-values for the least-square means are based on type III sum of squares. Differences were considered statistically significant for p-values less than 0.05. All statistical analyses were performed using the Statistical Analysis System (SAS) version 6.07 (27).

Results

The nurses ranged from 40 to 65 years of age with a mean age of 52.6. Means and standard deviations for the anthropometric variables were as follows: BMI = 24.4 ± 4.3, waist circumference = 78.5 ± 10.7 cm, hip circumference = 100.6 ± 9.65 cm, and WHR = 0.779 ± 0.07. Unadjusted Spearman correlations (Table 1) were positive between WHR and age (r=0.21; p=0.0001), and WHR and BMI (r=0.39; p=0.0001). Waist (r=0.20; p=0.0001) and hip circumference (r=0.10; p=0.0001) were also positively correlated with age and highly and similarly correlated with BMI (r=0.79; p=0.0001). Correlations between the anthropometric variables and the reproductive factors were low but highly statistically significant because of the large sample size. Age at menopause and parity were positively correlated and age at menarche was inversely correlated with BMI, waist and hip circumference. Duration of HRT and age at first birth were inversely correlated with BMI but positively correlated with waist circumference, hip circumference, and WHR.

Table 1. Spearman correlations* between anthropometric variables and reproductive factors

	BMI	Waist	Hip	WHR
Age (y)	0.10	0.20	0.10	0.21
Height (m)	-0.06	0.16	0.24	-0.00
BMI (wt(kg)/ht(m)^2)	1.00	0.79	0.79	0.39
Age at menopause† (y)	0.09	0.08	0.06	0.05
HRT‡ duration (months)	-0.02	0.02	0.01	0.03
Age at menarche (y)	-0.12	-0.05	-0.07	-0.00
Parity	0.09	0.11	0.06	0.10
Age at first birth (y)	-0.01	0.03	0.00	0.05

* $p < 0.05$ for all correlations except for correlations between WHR and height, WHR and age at menarche, and hip and age at first birth.
† Correlations calculated for naturally menopausal women only.
‡ HRT denotes hormone replacement therapy.

Menopausal Status

BMI was significantly lower and waist circumference was significantly greater in premenopausal women compared to naturally postmenopausal women who were never users of hormones. Both of these relations became nonsignificant after adjustment for smoking status, alcohol intake and physical activity (Table 2).

BMI was higher in women with a later age at menopause adjusting for age, smoking status, alcohol intake, physical activity, and HRT. A significant inverse association between age at menopause and WHR was driven by a small number of women with a very early age at menopause.

BMI was significantly higher in women who underwent surgical menopause compared to naturally menopausal women (BMI = 24.07 for natural

Table 2. Least square means (SEE*) for anthropometric variables†, by characteristics of menopause

Characteristic	%‡	BMI adjusted for age & WHR	Adjusted§ BMI	Waist (cm) adjusted for age, HT & BMI	Adjusted§ waist	WHR adjusted for age & BMI	Adjusted§ WHR
Menopausal Status							
premenopausal	35.8	24.11 (0.002)	24.06 (0.002)	77.30 (0.0008)	77.38 (0.0008)	0.773 (0.0009)	0.774 (0.0009)
postmenopausal**	31.5	23.92 (0.002)	23.98 (0.002)	77.55 (0.0008)	77.51 (0.0008)	0.774 (0.0009)	0.773 (0.0009)
-		$p = 0.006$	$p = 0.27$	$p = 0.02$	$p = 0.23$	$p = 0.24$	$p = 0.64$
Age at Menopause*** (y)							
<35	0.5	23.75 (0.02)	24.01 (0.02)	80.65 (0.008)	80.82 (0.008)	0.810 (0.009)	0.810 (0.009)
35-39	1.4	23.40 (0.01)	24.11 (0.01)	78.54 (0.005)	78.63 (0.005)	0.783 (0.006)	0.784 (0.005)
40-44	6.5	23.78 (0.005)	23.94 (0.005)	78.97 (0.002)	78.94 (0.002)	0.786 (0.003)	0.786 (0.003)
45-49	33.5	24.03 (0.002)	24.11 (0.002)	79.07 (0.001)	79.03 (0.001)	0.785 (0.001)	0.784 (0.001)
50-54	50.5	24.35 (0.002)	24.31 (0.002)	78.82 (0.0008)	78.86 (0.0008)	0.783 (0.0009)	0.783 (0.0009)
≥55	5.8	24.88 (0.005)	24.68 (0.005)	78.74 (0.002)	78.94 (0.002)	0.782 (0.003)	0.785 (0.003)
		p_t¶ = 0.0001	$p_t = 0.0001$	$p_t = 0.02$	$p_t = 0.15$	$p_t = 0.004$	$p_t = 0.06$

* SEE denotes standard error of the measurement and corresponds to the logarithm-tranformed means for waist and hip circumference. To calculate 95% confidence limits: $e^{(\ln \text{mean} \pm 1.96\text{SEM})}$.
† BMI = body mass index [weight (kg) / height $(m)^2$]; HT = height; WHR = waist circumference / hip circumference.
‡ Some frequencies do not add to 100% due to restrictions or missing values.
§ Means are adjusted for smoking, alcohol intake and physical activity in addition to age and the anthropometric variables specified in the column heading to the left. Means for age at menopause are also adjusted for postmenopausal hormone use.
** Analyses use women reporting natural menopause and never use of HRT only.
*** Analyses use women reporting natural menopause only.
¶ p_t indicates p value for trend.

menopause; BMI = 24.69 for bilateral oophorectomy; BMI = 24.47 for unilateral oophorectomy; BMI = 24.46 for hysterectomy without oophorectomy; $p < 0.0001$ for natural menopause versus each of the types of surgical menopause) controlling for age, WHR, age at menopause, HRT, smoking, alcohol, and physical activity. Adjusting for the same covariates, in contrast, WHR was significantly lower in women who had a natural menopause compared to women who had either a bilateral oophorectomy (WHR = 0.781 vs. 0.784, respectively, $p = 0.002$), or a hysterectomy without an oophorectomy (WHR = 0.781 vs. 0.783, $p = 0.04$). Similarly, adjusted waist circumference was also significantly lower for natural menopause than for bilateral oophorectomy and hysterectomy without oophorectomy (waist circumference = 78.69 vs. 78.91, $p = 0.04$ and 78.92, $p = 0.04$, respectively).

Hormone Replacement Therapy

Tables 3 and 4 present only the adjusted means. Mean BMI, waist circumference and WHR were significantly lower in current users of HRT, followed by past and never users, respectively (Table 3). The majority of women who were current users of HRT reported using either premarin (67.7%) or a sequential estrogen and progesterone combination (21.8%). Unopposed estrogen users were significantly heavier than users of estrogen and progesterone, although adjusting for type of menopause in addition to smoking, alcohol, and physical activity reduced this difference because hysterectomy was both more prevalent in the heavier women and associated with subsequent use of unopposed estrogens. Duration of HRT was not related to any of the anthropometric variables.

Other Reproductive Characteristics

Age at menarche was negatively associated with BMI and positively associated with waist circumference and WHR (Table 4). Parity was positively associated with BMI, waist circumference, and WHR. Adjusting for age at first birth, breast-feeding, smoking status, alcohol intake, and physical activity did not change the results for parity. WHR and waist circumference were significantly greater among women whose age at first birth was 30 years or greater compared to women under 30 years of age, and adjusting for parity, breast-feeding, smoking, alcohol and physical activity strengthened the results. Duration of breast-feeding was positively associated with BMI (p for trend = 0.0001); however, the association did not remain statistically significant after adjustment for covariates. No association with waist circumference and a positive association with hip circumference (p for trend = 0.0001) resulted in an inverse relation between breast-feeding and WHR that was

Table 3. Least square means (SEE*) for anthropometric variables† by postmenopausal hormone use

Characteristic	%‡	Adjusted§ BMI	Adjusted§ Waist (cm)	Adjusted§ WHR
Hormone Use				
never	48.4	24.69 (0.001)	79.21 (0.0007)	0.787 (0.0008)
current	27.9	23.64 (0.002)	78.66 (0.0009)	0.778 (0.001)
past	22.8	24.27 (0.002)	79.03 (0.0001)	0.784 (0.001)
Type**				
premarin	67.7	23.68 (0.002)	77.02 (0.001)	0.771 (0.001)
estrogen &	21.8	23.50 (0.003)	76.89 (0.002)	0.771 (0.002)
progesterone		$p = 0.06$	$p = 0.41$	$p = 0.82$
Duration** (y)				
<5	49.6	23.66 (0.002)	77.05 (0.001)	0.772 (0.001)
5-9	24.5	23.69 (0.003)	77.06 (0.001)	0.771 (0.002)
>10	22.8	23.62 (0.003)	76.99 (0.002)	0.770 (0.002)
		p_t¶ = 0.75	$p_t = 0.72$	$p_t = 0.26$

* SEE denotes standard error of the estimate and corresponds to the logarithm-transformed means for waist and hip circumference. To calculate 95% confidence limits: $e^{(\ln \text{mean} \pm 1.96\text{SEM})}$.

† BMI = body mass index [weight (kg) / height (m)^2]; WHR = waist circumference / hip circumference

‡ Some frequencies do not add to 100% due to missing values.

§ Means are adjusted for smoking, alcohol intake, and physical activity in addition to age and the anthropometric variables. Means for the hormone use and type analyses are also adjusted for type of menopause.

** Analyses performed in current users of HRT.

¶ p_t indicates p value for trend.

unchanged by adjustment for covariates. To determine if duration of breast-feeding modified the association of parity and WHR, an interaction term was added to a linear regression model including age, BMI, parity, and breast-feeding but was not significant ($p=0.55$). History of infertility was not related to any of the anthropometric measures.

To illustrate the magnitude of the association between HRT and WHR, a logistic regression with high WHR (defined as the upper fifth of the distribution) as the outcome was performed adjusting for age, BMI, type of menopause, smoking, alcohol intake, and physical activity. The odds of being in the highest quintile of WHR versus the lowest quintile of WHR for current postmenopausal hormone users was 0.67 (confidence limits = 0.60, 0.74) and for past users was 0.94 (0.83, 1.06) compared to never users. Similarly, the odds of being in the highest versus lowest quintile of WHR for bilateral oophorectomy was 1.15 (1.01, 1.31), for unilateral oophorectomy was 1.10 (0.91, 1.34), and for hysterectomy without oophorectomy was 1.09 (0.97, 1.22) compared to natural menopause.

Discussion

We investigated the relation of body fat distribution as measured by waist-to-hip ratio to several reproductive characteristics in a large study of pre- and postmenopausal women. After adjusting for several potential confounders, we found no association between menopausal status and WHR; however, women who experienced a natural menopause had a significantly smaller WHR than women who had undergone surgical menopause independent of hormone replacement therapy. In addition, women who were currently using replacement hormones had a significantly smaller WHR than women who were past or never users, although no association was noted between type and duration of hormone therapy and WHR. WHR demonstrated weak positive associations with age at menarche, parity and age at first birth, and a weak inverse association with duration of breast-feeding.

We hypothesized that low levels of endogenous female hormones associated with menopause would result in an increase in degree of central adiposity. Our findings, however, are consistent with other studies that have failed to find an association between menopausal status or age at menopause, and WHR after adjusting for age (2) and overall adiposity (15,32,13). WHR decreased slightly with increasing age at menopause but this relationship appeared to be driven by the small group of women who reported an age at natural menopause less than 35. In unadjusted analyses, age at natural menopause was not related to WHR in the DOM-project (31), a large cross-sectional study of Dutch women, and was weakly correlated with WHR in the Iowa Women's Health Study (13). Lanska et al.

Table 4. Means (SEE*) for anthropometric variables†, by reproductive factors

Characteristic	%‡	Adjusted§ BMI	Adjusted§ Waist (cm)	Adjusted§ WHR
Age at Menarche (y)				
<=11	20.9	24.91 (0.002)	77.62 (0.0007)	0.773 (0.0009)
12	26.0	24.22 (0.001)	77.87 (0.0006)	0.776 (0.0008)
13	31.5	23.89 (0.001)	77.90 (0.0006)	0.776 (0.0007)
14	12.8	23.57 (0.002)	78.07 (0.0009)	0.778 (0.001)
>=15	8.2	23.38 (0.002)	77.84 (0.001)	0.778 (0.001)
		p_t** = 0.0001	$p_t = 0.0002$	$p_t = 0.0001$
Parity				
0	6.7	24.05 (0.004)	77.00 (0.002)	0.765 (0.002)
1	7.1	23.96 (0.003)	77.41 (0.001)	0.771 (0.001)
2	27.5	23.92 (0.001)	77.67 (0.0006)	0.773 (0.0007)
3	27.3	24.09 (0.001)	77.80 (0.0006)	0.776 (0.0008)
4	16.2	24.23 (0.002)	78.14 (0.0008)	0.780 (0.001)
5	7.6	24.38 (0.003)	78.32 (0.001)	0.781 (0.001)
>=6	6.3	24.53 (0.003)	78.79 (0.001)	0.788 (0.002)
		$p_t = 0.0001$	$p_t = 0.0001$	$p_t = 0.0001$
Age at First Birth (y)				
<30	91.1	24.12 (0.0008)	77.85 (0.0004)	0.776 (0.0004)
>=30	8.8	24.14 (0.003)	78.41 (0.001)	0.781 (0.001)
		p = 0.78	p = 0.0001	p = 0.0001
Breast-feeding (months)				
0	32.8	24.09 (0.001)	77.92 (0.0006)	0.779 (0.0007)
0 - 6	38.3	24.14 (0.001)	77.93 (0.0006)	0.776 (0.0007)
>6	28.5	24.13 (0.001)	77.80 (0.0007)	0.773 (0.0008)
		$p_t = 0.65$	$p_t = 0.16$	$p_t = 0.0001$
Infertility				
no	85.6	24.13 (0.0008)	77.88 (0.0004)	0.776 (0.0004)
yes¶	4.8	24.08 (0.003)	77.99 (0.001)	0.777 (0.002)
		p = 0.58	p = 0.34	p = 0.53

* SEE denotes standard error of the estimate and corresponds to the logarithm-transformed means for waist and hip circumference. To calculate 95% confidence limits: $e^{(\ln \text{mean} \pm 1.96\text{SEM})}$.
† BMI = body mass index [weight (kg) / height $(m)^2$]; WHR = waist circumference / hip circumference.
‡ Some frequencies do not add to 100% due to missing values.
§ Means are adjusted for smoking, alcohol intake, and physical activity in addition to age and the anthropometric variables. Means for parity, age at first birth, and breast-feeding are adjusted for each other.
** p_t indicates p value for trend.
¶ Analyses performed using women indicating source of infertility was self.

(15), in members of the TOPS study, found no relation between WHR and age at menopause after adjusting for age, current percent above ideal body weight, and the greatest percent above ideal body weight achieved while a teenager.

Adjusting for age and BMI, women who underwent surgical menopause had a slightly higher WHR compared to women who experienced a natural menopause. This difference was greatest for bilateral oophorectomy. Since surgically menopausal women were more likely to use replacement hormones, and HRT was inversely associated with WHR, adjusting for HRT increased the magnitude of the difference. Kaye and colleagues (13) also found that women with a surgical menopause had a greater WHR. The sudden decrease in endogenous female hormone levels associated with removal of both ovaries may explain why these women had more fat distributed centripetally than naturally menopausal women, who may experience a more gradual decline in ovarian hormone production.

As expected, current use of hormone replacement therapy was associated with a significantly lower WHR after adjusting for age and BMI. Earlier cross-sectional studies have reported similar findings (13,31). Bias could explain these results if women with larger abdominal fat depots have more available endogenous estrogens making them less likely to experience symptoms and request hormone therapy (31). Data from a trial conducted in Denmark (9), however, provide some evidence for causality. Sixty-two postmenopausal women 45 to 55 years of age who had become menopausal 3 to 6 months earlier were randomized to combined estrogen-progesterone therapy or placebo and matched on menopausal age, height, weight, BMI, and lipid levels. Using dual photon absorptiometry to measure abdominal fat percentage, the investigators found that the untreated women increased their abdominal fat depot by 5.5% over 2 years of follow-up. The abdominal fat depot in the treated women, however, was unchanged. Furthermore, experimental data from studies conducted in postmenopausal women seem to support effects of replacement hormones on regional cell metabolism that would favor accumulation of fat in the femoral-gluteal area and inhibit fat accumulation in the abdomen. Combined estrogen and progesterone therapy has been shown to increase LPL activity of femoral but not abdominal adipocytes (23,22), with no effect on lipolysis in either region (22). In another study, increased LPL activity in femoral adipocytes following administration of ethinyl estradiol was blunted with the addition of norethisterone acetate, a potent androgenic progestogen (17). In addition, estradiol reduced lipolysis in the abdominal area. Thus, there is ample evidence to support a role for exogenous sex hormones in determining fat distribution although the effects of specific steroid hormones have not been delineated. In the present study, after adjusting for type of menopause the means for WHR were identical for users of unopposed and opposed estrogens. To our knowledge, no other epidemiologic study has assessed the effect of different types of hormone therapy on body fat distribution.

A positive association of WHR with age at menarche corroborates results from the Iowa Women's Health Study (13) although the magnitude of the relation was slightly larger in this investigation. On the contrary, age at menarche adjusted for age, BMI, and BMI squared was unrelated to WHR in the DOM-project (32,31). It is difficult to envision how an event taking place so early in life relates to adult distribution of body fat. Perhaps the hormonal milieu that leads to delayed menarche, specifically low endogenous estrogen levels, also results in a greater preponderance of centrally distributed fat at puberty. To the extent that fat distribution tracks over time, this could explain the association of age at menarche with adult fat distribution. Additionally, women with a late age at menarche may differ in their adult hormonal profile from women whose menarche occurred at an earlier age. In a study of women 21 to 30 years of age, follicular phase serum estradiol concentrations were higher and sex hormone binding globulin concentrations were lower among women who had an early menarche (1), although not all studies have confirmed this observation (3,12). It is also unknown whether hormonal profile continues to differ among older premenopausal women.

Previous studies have reported linear and J-shaped (13) relationships of parity to WHR. In the present study, WHR increased monotonically with each sucessive child. These results are not consistent with clinical data demonstrating that in early pregnancy, LPL activity is much greater for femoral than abdominal adipocytes (21). An alternative explanation for these data may be that multiple pregnancies result in weakened stomach muscles (15).

The results for age at first birth are consistent with Kaye et al. (13) who found that despite a lower BMI, WHR was higher in women whose age at first birth was greater than 30 compared to women giving birth before age 30. Rodin and colleagues (26) have reported that in women, a high WHR is associated with a greater degree of weight cycling. Perhaps the effect of weight change on WHR is modified by age at which weight gain occurs. Older women experiencing weight change associated with pregnancy may tend to increase their WHR more than women experiencing weight change from pregnancy at an earlier age. Alternatively, increased abdominal adiposity may cause delayed childbirth. In a prospective study of women attending an infertility clinic for artificial insemination conducted in the Netherlands, an inverse association was found between WHR and the probability of conception per menstrual cycle (35). A 0.1 unit increase in WHR was associated with a relative risk of conception of 0.71 (confidence limits = 0.56, 0.89) adjusting for age, BMI, reasons for artificial insemination, cycle length and regularity, smoking, and parity. The hypothesis that WHR is associated with subfertility and is thus greater in women with a late age at first birth, however, is not supported by the positive association between WHR and parity observed in the present study. Furthermore, in our data and in those of Kaye et al. (13), WHR was not associated with history of infertility. Misclassification could have caused us to miss an association with WHR, however, since self-report of infertility was not validated in the present study. This relationship deserves further investigation.

Hip circumference was positively associated with past duration of breast-feeding resulting in an inverse relation between breast-feeding and WHR. Adjusting for parity increased the strength of this association. The studies evaluating the effect of lactation on body fat distribution are few and their results are inconsistent (6,4). Dugdale and Eaton-Evans (6) followed 174 women up to 12 months postpartum and found no difference in weight or triceps skinfold between mothers who did and did not breast-feed their children. Brewer et al. (4), in a study of 56 women followed 6 months postpartum, found that compared to measures taken at delivery, triceps, subscapular, and suprailiac skinfolds were increased after 3 months in all women regardless of whether they breast-fed, formula-fed or used a combination of breast milk and formula. At 6 months, however, triceps skinfold, a measure of peripheral adiposity, remained significantly elevated in the breast-feeding mothers only. Effects of lactation on regional fat cell metabolism have been reported (21). LPL activity in lactating women has been shown to be significantly lower in the femoral region than in the abdominal region, and basal lipolysis, in contrast, to be significantly greater. While these data are not consistent with the direction of the association between breast-feeding and WHR demonstrated in the present study, the long-term effects of lactation on cell metabolism are unknown.

The question of which measure best represents central adiposity remains controversial. We chose to use the ratio of abdomen (measured at the umbilicus) to hip circumference because it has been shown to correlate better with total area of intraabdominal fat as measured by CT scans than waist (measured at the minimum circumference) to hip circumference ratio (30). Self-report of circumferences resulted in some degree of measurement error, although technician-measured and self-measured waist and hip circumferences were highly correlated in a subsample of this cohort (25). If measurement error were random with respect to the lifestyle and reproductive factors assessed in these analyses, then the estimates of the means should be unbiased and the resulting increase in the standard errors of the means would only act to reduce our ability to demonstrate statistically significant differences. This was not a problem due to the large sample size which caused small differences in the anthropometric variables to be highly statistically significant. In addition, because of the small magnitude of the associations reported in this paper, we cannot exclude the possibility that these results are explained by factors not measured in this study.

In conclusion, several reproductive characteristics and use of hormone replacement therapy were related to WHR in this large study of pre- and postmenopausal women. Research evaluating the association of body fat distribution to diseases related to reproductive factors, in particular, cardiovascular disease and the reproductive cancers, should consider these factors as potential confounders.

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References

1. **Apter D, Reinila M, Vihko R.** Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. *Int J Cancer.* 1989;44:783-787.
2. **Armellini F, Micciolo R, Ferrari P, et al.** Blood pressure, metabolic variables and adipose tissue distribution in pre-and post-menopausal women. *Acta Obstet Gynecol Scand.* 1990;69:627-633.
3. **Bernstein L, Pike MC, Ross RK, Henderson BE.** Age at menarche and estrogen concentrations of adult women. *Cancer Causes Cont.* 1991;2:221-225.
4. **Brewer MM, Bates MR, Vannoy LP.** Postpartum changes in maternal weight and body fat depots in lactating vs. nonlactating women. *Am J Clin Nutr.* 1989;49:259-265.
5. **Colditz GA, Stampfer MJ, Willett WC, et al.** Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol.* 1987;126:319-325.
6. **Dugdale AE, Eaton-Evans J.** The effect of lactation and other factors on post-partum changes in body-weight and triceps skinfold. *Br J Nutr.* 1989;61:149-153.
7. **Folsom AR, Kaye SA, Sellers TA, et al.** Body fat distribution and 5-year risk of death in older women. *JAMA.* 1993;289: 483-487.
8. **Giovannucci E, Colditz G, Stampfer MJ, et al.** The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol.* 1991;133:810-817.
9. **Haarbo J, Marslew U, Gotfredsen A, Christiansen C.** Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism.* 1991;40:1323-1326.
10. **Haffner SM, Katz MS, Dunn JF.** Increased upper body and overall adiposity is associated with decreased sex hormone binding globulin in postmenopausal women. *Int J Obes.* 1991;15:471-478.
11. **Hartz AJ, Rupley DC, Kalkhoff RD, Rimm AA.** Relationship of obesity to diabetes: influence of obesity level and body fat distribution. *Prev Med.* 1983;12:351-357.
12. **Ingram DM, Nottage EM, Willcox EL, Roberts A.** Oestrogen binding and risk factors for breast cancer. *Br J Cancer.* 1990;61:303-307.
13. **Kaye SA, Folsom AR, Prineas RJ, Potter JD, Gapstur SM.** The association of body fat distribution with lifestyle and reproductive factors in a population study of postmenopausal women. *Int J Obes.* 1990;14:583-591.
14. **Khaw K-T, Barrett-Connor E.** Lower endogenous androgens predict central adiposity in men. *Ann Epidemiol.* 1992;2:675-682.
15. **Lanska DJ, Lanska MJ, Hartz AJ, Rimm AA.** Factors influencing the anatomic location of fat tissue in 52,953 women. *Int J Obes.* 1985;9:29-38.

16. **Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G.** Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *BMJ.* 1984;288:1401-1404.
17. **Lindberg U-B, Crona N, Silfverstolpe G, Bjorntorp P, Rebuffe-Scrive M.** Regional adipose tissue metabolism in postmenopausal women after treatment with exogenous sex steroids. *Horm Metab Res.* 1990;22:345-351.
18. **Ohlson L-O, Larsson B, Svardsudd K, et al.** The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes.* 1985;34:1055-1058.
19. **Peiris AN, Sothmann MS, Hoffmann RG, et al.** Adiposity, fat distribution, and cardiovascular risk. *Ann Intern Med.* 1989;110: 867-872.
20. **Rebuffe-Scrive M, Eldh J, Hafstrom L-O, Bjorntorp P.** Metabolism of mammary, abdominal and femoral adipocytes in women before and after menopause. *Metabolism.* 1986;35:792-797.
21. **Rebuffe-Scrive M, Enk L, Crona N, et al.** Fat cell metabolism in different regions in women: effect of menstrual cycle, pregnancy, and lactation. *J Clin Invest.* 1985;75:1973-1976.
22. **Rebuffe-Scrive M, Lonnroth P, Marin P, Wesslau C, Bjorntorp P, Smith U.** Regional adipose tissue metabolism in men and postmenopausal women. *Int J Obes.* 1987;11:347-355.
23. **Rebuffe-Scrive M, Marin P, Bjorntorp P.** Effect of testosterone on abdominal adipose tissue in men. *Int J Obes.* 1991;15:791-795.
24. **Rebuffe-Scrive M.** Steroid hormones and distribution of adipose tissue. *Acta Med Scand Suppl.* 1988;723:143-146.
25. **Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC.** Validity of self-reported waist and hip circumferences in men and women. *Epidemiology.* 1990;1:466-473.
26. **Rodin J, Radke-Sharpe N, Rebuffe-Scrive M, Greenwood MRC.** Weight cycling and fat distribution. *Int J Obes.* 1990;14:303-310.
27. **SAS Institute Inc.** SAS user's guide: statistics, version 6.07 edition. Cary, NC: Statistical Analysis System Institute Inc; 1990.
28. **Seidell JC, Cigolini M, Charzewska J, et al.** Androgenicity in relation to body fat distribution and metabolism in 38-year-old women: the European fat distribution study. *J Clin Epidemiol.* 1990;43:21-34.
29. **Seidell JC, Cigolini M, Deurenberg P, Oosterlee A, Doornbos G.** Fat distribution, androgens, and metabolism in nonobese women. *Am J Clin Nutr.* 1989;50:269-273.
30. **Seidell JC, Oosterlee A, Thijssen MAO, et al.** Assessment of intra-abdominal and subcutaneous abdominal fat: relation between anthropometry and computed tomography. *Am J Clin Nutr.* 1987;45:7-13.
31. **den Tonkelaar I, Seidell JC, van Noord PAH, Baanders-van Halewijn EA, Jacobus JH, Bruning PF.** Factors influencing waist/hip ratio in randomly selected pre- and post-menopausal women in the DOM-project (preliminary results). *Int J Obes.* 1989;13:817-824.
32. **den Tonkelaar I, Seidell JC, van Noord PAH, Baanders-van Halewijn EA, Ouwehand IJ.** Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use: a cross-sectional study in 11,825 Dutch women participating in the DOM-project. *Int J Obes.* 1990;14:753-761.
33. **Willett WC, Stampfer M, Bain C, et al.** Cigarette smoking, relative weight, and menopause. *Am J Epidemiol.* 1985;117:651-658.
34. **Wolf AM, Hunter DJ, Colditz GA, et al.** Reproducibility and validity of a self-administered physical activity questionnaire in the Nurses' Health Study II. *Int J Epidemiol.* 1994;23:991-999.
35. **Zaadstra BM, Seidell JC, Van Noord PAH, et al.** Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *BMJ.* 1993;306:484-487.